REMARKS

Claims 22-42 are pending. Claims 22-26, 41, and 42 are currently under examination, and claims 27-40 have been withdrawn from consideration due to a restriction requirement. Claim 25 is objected to because of informalities.

Claim 41 is rejected under 35 U.S.C. § 102(b) as being anticipated by Van Cauwenberghe et al. (*Heterocycles*, 1975, 3:101-107; hereafter "Van Cauwenberghe"), by May et al. (*J. Pharmaceutical Sciences*, 1968, 57:511-513; hereafter "May"), by Guidi et al. (*Arch. Pharm. Pharm. Med. Chem.*, 1997, 330:201-202; hereafter "Guidi"), by Wang et al. (*J. Chem. Soc., Perkin Trans.*, 1996, 1:209-212; hereafter "Wang"), and by Guerret et al. (US 4,463,004; hereafter "Guerret"). Claims 22-24 and 26 are also rejected under 35 U.S.C. § 102(b) as being anticipated by Guerret.

Claim 41 is rejected under 35 U.S.C. § 103 for obviousness over Cauwenberghe, May, Guidi, Wang, or Guarna et al. (*Tetrahedron: Asymmetry*, 2000, 11:4227-4238; hereafter "Guarna-2000"). Claims 41 and 42 are rejected under 35 U.S.C. § 103 as being obvious in view of Guarna et al. (WO 01/64686; hereafter "Guarna-2001"), Guarna et al. (US 2003/0176414; hereafter "Guarna-2003"), Scarpi et al. (*Bioorg. Med. Chem.*, 2001, 9:1625-1632; hereafter "Scarpi"), or Machetti et al. (*Org. Lett.*, 2000, 2:3987-3990; hereafter "Machetti"). Claims 22-26 are rejected under 35 U.S.C. § 103 as being obvious in view of Guarna-2001 or Guarna-2003. Claims 22-24, 26, and 41 are rejected under 35 U.S.C. § 103 as being obvious in view of Guerret. Claims 22-26, 41, and 42 are rejected under 35 U.S.C. § 103 as being obvious in view of Guarna et al. (*J. Org. Chem.*, 1999, 64:7347-7364; hereafter "Guarna-1999").

Lastly, claims 22-26, 41, and 42 are provisionally rejected on the ground of nonstatutory

obviousness-type double patenting as being unpatentable over claims 1-5 of co-pending Application No. 10/220,556 (published as US 2003/0176414; hereafter " '556").

The objection and rejections are addressed below.

Amendments to the Claims

Claim 22 has been amended to require the use of the claimed pharmaceutical compositions for the treatment of diseases in which neurotrophine functions are involved in defect. Support for this amendment can be found, for example, on page 1, line 30 through page 2, line 3, and on page 2, lines 5-10, of the Specification. Claim 25 has been amended to correct informalities. Support for this amendment can be found, e.g., on pages 45-61 of the Specification. Claim 41 has been amended to further exclude the compound of formula (I) wherein Z = Y = O, X = R_2 = R_3 = R_4 = R_5 = H, R_1 = Me, and R_6 = CH_2NMe_2; the compound of formula (I) wherein Z=Y=O, X= R_1=R_2=R_4=R_5=R_6=H, and R_3=Me; the compound of formula (I) wherein X=Y=Z=O, R_1=R_4=R_5=H, R_2 is CH_2Ph, R_3 is CH_2PhOMe, and R_6 is COOMe; the compound of formula (I) wherein X=Y=Z=O, R_1=Ph, R_2=R_4=R_5=H, R_3 is Me, and R_6 is Ph; and the compounds of formula (I) wherein R_6 is H. Support for this amendment is found, for example, on page 3, lines 13-16, page 24, lines 5-11, and generally on page 2, line 11 through page 4, line 9 of the Specification.

Claim Objections

The Examiner has objected to claim 25 because of informalities. We have corrected the substituent of compound 127, formatted the chemical notation uniformly by italicizing all

characters indicating compound stereochemistry, and have aligned the rows of each table. Applicants respectfully request that this objection be withdrawn.

Rejections Under 35 U.S.C. § 102(b)

Van Cauwenberghe

Claim 41 is rejected under 35 U.S.C. § 102(b) as being anticipated by Van Cauwenberghe. The Examiner asserts that, in compound III on page 106, Van Cauwenberghe teaches the claimed compound of formula (I) where X is H: Y and Z are O; R_1 is C_1 alkyl; R_2, R_3, R_4, and R_5 are H; and R_6 is CH_2NRR', where R and R' are C_1 alkyl. Applicants have amended claim 41 to disclaim the compound of formula (I) wherein Z = Y = O, X = R_2 = R_3 = R_4 = R_5 = H, R_1 = Me, and R_6 = CH_2NMe_2. The remaining compounds of formula (I) are not anticipated by Van Cauwenberghe. Furthermore, Van Cauwenberghe discloses compounds, their preparation, and spectroscopic analysis, without reference to their properties, including the specific pharmaceutical activity found by the Applicants; thus the remaining compounds of formula (I) are novel. Applicants respectfully request that this rejection be withdrawn.

May

Claim 41 is rejected under 35 U.S.C. § 102(b) as being anticipated by May. The Examiner asserts that, in *N*-methyl-6,8-dioxa-3-azabicyclo[3.2.1]-octane on page 512, column 1, May teaches the claimed compound of formula (I) wherein X is H; Y and Z are O; R_1, R_2, R_4, R_5, and R_6 are H; and R_3 is C_1 alkyl. Applicants have amended claim 41 to disclaim the compound

of formula (I) wherein Z=Y=O, X= R_1=R_2=R_4=R_5=R_6=H, and R_3=Me. The remaining compounds of formula (I) are not anticipated by May. Furthermore, May does not disclose any properties, including pharmacological activity, of this compound, but on the contrary, May discloses this compound as a reaction intermediate, immediately quaternarised to another compound, which differs from that of formula (I) because it has a quaternary ammonium group; thus the remaining compounds of formula (I) are novel. Applicants respectfully request that this rejection be withdrawn.

Guidi

Claim 41 is rejected under 35 U.S.C. § 102(b) as being anticipated by Guidi. The Examiner asserts that, in compound 3 on page 201, Guidi teaches the claimed compound of formula (I) wherein X, Y, and Z are O; R_1, R_4, and R_5 are H; R_2 and R_3 are aryl C_1 alkyl; and R_6 is C(O)OR, wherein R is C_1 alkyl. Applicants have amended claim 41 to disclaim the compound of formula (I) wherein X=Y=Z=O, R_1=R_4=R_5=H, R_2 is CH_2Ph, R_3 is CH_2PhOMe, and R_6 is COOMe. The remaining compounds of formula (I) are not anticipated by Guidi. Furthermore, Guidi does not disclose any specific pharmacological properties of this compound, but only refers to a hypothetical generic utility of this kind of compounds for recognition of peptide receptor sites; thus the remaining compounds of formula (I) are novel. Applicants respectfully request that this rejection be withdrawn.

Wang

Claim 41 is rejected under 35 U.S.C. § 102(b) as being anticipated by Wang. The

Examiner asserts that, in compound 12 on page 210, Wang teaches the compound of formula (I) wherein X, Y, and Z are O; R_2, R_4, and R_5 are H; R_1 and R_6 are aryl; and R_3 is C_1 alkyl. Applicants have amended claim 41 to disclaim the compound of formula (I) wherein X=Y=Z=O, R_1=Ph, R_2=R_4=R_5=H, R_3 is Me, and R_6 is Ph. The remaining compounds of formula (I) are not anticipated by Wang. Furthermore, Wang discloses this compound only as an intermediate in a process for preparing another compound, a liver-protecting agent, which is distinct from this compound; thus the remaining compounds of formula (I) are novel. Applicants respectfully request that this rejection be withdrawn.

Guerret

Claims 22-24, 26, and 41 are rejected under 35 U.S.C. § 102(b) as being anticipated by Guerret. The Examiner asserts that, in claim 1 and Table I, Guerret teaches many compounds of formula (I), wherein X is H, Y and Z are O, R_2, R_4, R_5, and R_6 are H, R_1 is H, alkyl having at least 4 carbons, cyclohexyl, or aryl, and R_3 is C_1 to C_4 alkyl, cyclohexyl, or benzyl. Applicants have amended claim 41 to disclaim all compounds of formula (I) wherein R_6 is H. The remaining compounds of formula (I) are not anticipated by Guerret. Applicants respectfully request that this rejection be withdrawn.

The Examiner further asserts that, in column 17, lines 12 through column 18, line 15, Guerret teaches that the compounds have "pharmacological properties", particularly "analgesic activity", and that the compounds can be prepared as pharmaceutical compositions for administration as analgesics. Applicants have amended claim 22 to recite that the pharmaceutical composition comprising a compound of formula (I) is "for use in the treatment of

diseases in which neurotrophine functions are involved in defect." Guerret does not disclose neurotrophine activity of these compounds; therefore, the amended claims are not anticipated. Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

Van Cauwenberghe

Claim 41 is rejected under 35 U.S.C. § 103 for obviousness over Van Cauwenberghe. The Examiner asserts that, in compound III on page 106, Van Cauwenberghe teaches the compound of formula (I) wherein X is H, Y and Z are O, R_1 is C_1 alkyl, R_2, R_3, R_4, and R_5 are H, R_6 is CH_2NRR', wherein R and R' are C_1 alkyl such that the "adjacent" compounds of formula (I) wherein X is H, Y and Z are O, R_1 is C_1 alkyl, R_2, R_3, R_4, and R_5 are H, and R_6 is CH_2NRR', wherein R_1, R, or R' are greater than C_1 alkyl are obvious.

Applicants respectfully disagree. Firstly, as previously discussed, Applicants have disclaimed compounds of formula (I) wherein X is H, Y and Z are O, R_1 is C_1 alkyl, R_2, R_3, R_4, and R_5 are H, R_6 is CH_2NRR', wherein R and R' are C_1 alkyl. Secondly, as the Office notes, "adjacent homologs are considered to be obvious absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art" (page 7 and 8). The claimed "adjacent" compounds of formula (I) possess an unexpected pharmacological activity, e.g., as neurotrophine agonists, that is not disclosed or suggested by Van Cauwenberghe, thus the claimed "adjacent" compounds of formula (I) cannot be obvious because they have unexpected properties. Applicants respectfully request that this rejection be withdrawn.

May

Claim 41 is rejected under 35 U.S.C. § 103 for obviousness over May. The Examiner asserts that, on page 512, column 1, May teaches the compound of formula (I) wherein X is H, Y and Z are O, R_1, R_2, R_4, R_5, and R_6 are H, and R_3 is C_1 alkyl such that the "adjacent" compounds of formula (I) wherein X is H, Y and Z are O, R_1, R_2, R_4, R_5, and R_6 are H, and R_3 is greater than C_1 alkyl are obvious.

Applicants respectfully disagree. Firstly, as previously discussed, Applicants have disclaimed compounds of formula (I) wherein X is H, Y and Z are O, R_1, R_2, R_4, R_5, and R_6 are H, and R_3 is C_1 alkyl. Secondly, the Office has noted that "adjacent homologs are considered to be obvious absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art" (page 7 and 8). The claimed "adjacent" compounds of formula (I) possess an unexpected pharmacological activity, e.g., as neurotrophine agonists, that is not disclosed or suggested by May, thus the claimed "adjacent" compounds of formula (I) cannot be obvious because they have unexpected properties. Lastly, May teaches away from the present invention, because it teaches that azabicyclo[3.2.1.]octane derivatives have negligible activity and that azabicyclo[3.2.1.]octane derivatives preferably have a quaternary ammonium group, known to be beneficial for binding to acetylcholine receptors (i.e. muscarinic and nicotinic receptors) and for affecting the nervous system, which is not present in the claimed compounds of formula (I). In support of this point, on page 512, Table I and page 513, column 1, lines 3-6, May teaches that the tested compounds II, III, and IV "were found to

have negligible activities at both muscarinic and nicotinic receptors," and on page 513, column 1, paragraph *Discussion*, lines 1-3, May teaches that compound II (which is the most similar to the present compounds of formula (I)) "is apparently devoid of muscarinic activity." Thus, May teaches away from the claimed compounds and the claimed compounds cannot be obvious. Applicants respectfully request that this rejection be withdrawn.

Guidi

Claim 41 is rejected under 35 U.S.C. § 103 for obviousness over Guidi. The Examiner asserts that, in compound 3 on page 201, Guidi teaches the compound of formula (I) wherein X, Y, and Z are O, R_1, R_4, and R_5 are H, R_2 and R_3 are aryl C_1 alkyl, and R_6 is C(O)OR, wherein R is C_1 alkyl such that the "adjacent" compounds of formula (I) wherein X, Y, and Z are O, R_1, R_4, and R_5 are H, R_2 and R_3 are aryl alkyl with alkyl greater than C_1, and R_6 is C(O)OR, where R is greater than C_1 alkyl are obvious.

Applicants respectfully disagree. Firstly, as previously discussed, Applicants have disclaimed compounds of formula (I) wherein X, Y, and Z are O, R_1, R_4, and R_5 are H, R_2 and R_3 are aryl C_1 alkyl, and R_6 is C(O)OR, wherein R is C_1 alkyl. Secondly, the Office has noted that "adjacent homologs are considered to be obvious absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art" (page 7 and 8). The claimed "adjacent" compounds of formula (I) possess an unexpected pharmacological activity, e.g., as neurotrophine agonists, that is not disclosed or suggested by Guidi, thus the claimed "adjacent" compounds of formula (I) cannot be obvious because they have unexpected

properties. Applicants respectfully request that this rejection be withdrawn.

Wang

Claim 41 is rejected under 35 U.S.C. § 103 for obviousness over Wang. The Examiner asserts that, in compound 12 on page 210, Wang teaches the compound of formula (I) wherein X, Y, and Z are O, R_2, R_4, and R_5 are H, R_1 and R_6 are aryl, and R_3 is C_1 alkyl such that the "adjacent" compounds of formula (I) wherein X, Y, and Z are O, R_2, R_4, and R_5 are H, R_1 and R_6 are aryl, and R_3 is greater than C_1 alkyl are obvious.

Applicants respectfully disagree. Firstly, as previously discussed, Applicants have disclaimed compounds of formula (I) wherein X, Y, and Z are O, R_2, R_4, and R_5 are H, R_1 and R_6 are aryl, and R_3 is C_1 alkyl. Secondly, the Office has noted that "adjacent homologs are considered to be obvious absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art" (page 7 and 8). The claimed "adjacent" compounds of formula (I) possess an unexpected pharmacological activity, e.g., as neurotrophine agonists, that is not disclosed or suggested by Wang, thus the claimed "adjacent" compounds of formula (I) cannot be obvious because they have unexpected properties. Applicants respectfully request that this rejection be withdrawn.

Guerret

Claims 22-24, 26, and 41 are rejected under 35 U.S.C. § 103 for obviousness over Guerret. The Examiner asserts that, in claim 1 and Table I, Guerret teaches the compound of

formula (I) wherein X is H, Y and Z are O, R_2, R_4, R_5, and R_6 are H, R_1 is H, alkyl having at least 4 carbons, cylcohexyl, or aryl, and R_3 is C_1 to C_4 alkyl, cyclohexyl, or benzyl such that the "adjacent" compounds of formula (I) wherein X is H, Y and Z are O, R_2, R_4, R_5, and R_6 are H, R_1 is alkyl having less than 4 carbons, and R_3 is greater than C_4 alkyl are obvious. The Examiner further asserts that, in column 17, line 12 through column 18, line 15, Guerret teaches that the compounds have "pharmacological properties," particularly "analgesic activity," and that the compounds may be prepared as pharmaceutical compositions such that pharmaceutical compositions containing the "adjacent" compounds are also obvious.

Applicants respectfully disagree. Firstly, as previously discussed, Applicants have disclaimed from claim 41 the compound of formula (I) wherein X is H, Y and Z are O, R_2, R_4, R_5, and R_6 are H, R_1 is H, alkyl having at least 4 carbons, cylcohexyl, or aryl, and R_3 is C_1 to C_4 alkyl, cyclohexyl, or benzyl. Secondly, the Office has noted that "adjacent homologs are considered to be obvious absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art" (page 7 and 8). The claimed "adjacent" compounds of formula (I) recited in claim 41 and the pharmaceutical compositions containing them recited in claims 22-24 and 26 possess an unexpected neurotrophine agonist activity that is not disclosed or suggested by Guerret, thus the claimed "adjacent" compounds of formula (I) and the pharmaceutical compositions containing them cannot be obvious because they have unexpected properties.

Furthermore, Applicants have amended claim 22 to recite a pharmaceutical composition "for use in the treatment of diseases in which neurotrophine functions are involved in defect,"

further discriminating the pharmaceutical compositions of claims 22-24 and 26 from Guerret. Particularly, on pages 27 and 28 of the Specification, Applicants state that the present compounds show neurotrophine agonist activity, especially of NGF, i.e., they have the property of inducing the biological signal of neurotrophines, and they are therefore suitable for use in pharmaceutical compositions to treat the listed diseases.

Other applications of these compounds are also reported on page 29 of the Specification, such as their use as reagents for promoting growth and/or *in* vivo, *in* vitro, or *ex* vivo survival of neuronal cells, or their use in the preparation of culture and storage media useful for conservation of explanted corneas destined for transplantations.

Furthermore, on pages 38-42 of the Specification, biological tests carried out on the present compounds are reported and should be considered by the Examiner. In particular, the biological activity of compounds of formula (I), (II), and (III) has been tested for the ability to induce survival of PC12 cells in serum-free conditions, for the single compound, and for multiple combinations of compounds to show their synergistic activity; the ability to induce proliferative activity in PC3 prostatic carcinoma cell line; the ability to induce VGF production by PC12 cells; the ability to displace the binding of NGF to specific surface receptor; and the ability to induce Trk-A autophosphorylation, triggering the transduction of biological signals.

These biological activities show that the present compounds have unexpected properties not disclosed or suggested in Guerret and, therefore, cannot be obvious because of these unexpected properties. Applicants respectfully request that this rejection be withdrawn.

Guarna-2001 as applied to claims 41 and 42

Claims 41 and 42 are rejected under 35 U.S.C. § 103 for obviousness in view of Guarna-2001. The Examiner asserts that, in compound 214 on page 43, Guarna-2001 teaches the instant compound 138 and 142 with undefined stereochemistry such that it would have been obvious to resolve the stereoisomers having substantially different pharmacological activity.

Applicants respectfully disagree. Firstly, the compounds disclosed by Guarna-2001 are already disclaimed from the present claims. Secondly, the Office has noted that "adjacent homologs are considered to be obvious absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art" (page 7 and 8). Guarna-2001 only refers to libraries of compounds, without disclosing or suggesting any pharmacological activities. Thus, the claimed compounds cannot be obvious because they contain unexpected properties, i.e., pharmacological activities, not disclosed or suggested by Guarna-2001. Applicants respectfully request that this rejection be withdrawn.

Guarna-2001 as applied to claims 22-26

Claims 22-26 are rejected under 35 U.S.C. § 103 for obviousness in view of Guarna-2001. The Examiner asserts that, in compound 214 on page 43, Guarna-2001 teaches the instant compound 138 and 142 with undefined stereochemistry and, on page 3, lines 9-11, that their compounds are used to "discover new leads for therapeutical applications" such that it would have been obvious to resolve the stereoisomers having substantially different pharmacological activity and prepare the resolved stereoisomers as pharmaceutical compositions.

Applicants respectfully disagree. Firstly, the compounds disclosed by Guarna-2001 are already disclaimed from the present claims. Secondly, the Office has noted that "adjacent homologs are considered to be obvious absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art" (page 7 and 8). Guarna-2001 only refers to libraries of compounds, without disclosing or suggesting any pharmacological activities, particularly that of neurotrophine agonists, thus the claimed pharmaceutical compositions cannot be obvious because they contain unexpected properties, i.e. pharmacological activities such as that of neurotrophine agonists, not disclosed or suggested by Guarna-2001. Applicants respectfully request that this rejection be withdrawn.

Guarna-2003 as applied to claims 41 and 42

Claims 41 and 42 are rejected under 35 U.S.C. § 103 for obviousness in view of Guarna-2003. The Examiner asserts that, as Guarna-2003 is a national stage entry of the international application Guarna-2001, the basis of this rejection is the same as that under Guarna-2001.

Applicants disagree for the reasons noted above. Firstly, the compounds already disclosed by Guarna-2003 are already disclaimed from the present claims. Secondly, the Office has noted that "adjacent homologs are considered to be obvious absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art" (page 7 and 8). Guarna-2003 only refers to libraries of compounds, without disclosing or suggesting any pharmacological activities, thus the claimed compounds cannot be obvious

because they contain unexpected properties, i.e. pharmacological activities, not disclosed or suggested by Guarna-2003. Applicants respectfully request that this rejection be withdrawn.

Guarna-2003 as applied to claims 22-26

Claims 22-26 are rejected under 35 U.S.C. § 103 for obviousness in view of Guarna-2003. The Examiner asserts that, as Guarna-2003 is a national stage entry of the international application Guarna-2001, the basis of this rejection is the same as that under Guarna-2001.

Applicants disagree for the reasons noted earlier. Firstly, the compounds already disclosed by Guarna-2003 are already disclaimed from the present claims. Secondly, the Office has noted that "adjacent homologs are considered to be obvious absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art" (page 7 and 8). Guarna-2003 only refers to libraries of compounds, without disclosing or suggesting any pharmacological activities, particularly that of neurotrophine agonists, thus the claimed pharmaceutical compositions cannot be obvious because they contain unexpected properties, i.e. pharmacological activities such as that of neurotrophine agonists, not disclosed or suggested by Guarna-2003. Applicants respectfully request that this rejection be withdrawn.

Guarna-2000

Claim 41 is rejected under 35 U.S.C. § 103 for obviousness in view of Guarna-2000. The Examiner asserts that, in compounds 11, 12, and 13 on page 4230, Guarna-2000 teaches the compounds 34, 58, and 177 of formula (I), as defined in claim 25, such that it would be obvious

to make and resolve the claimed compounds 35, 59, and 177, which are stereoisomers of compounds 34, 58, and 177.

Applicants respectfully disagree. Firstly, Applicants have disclaimed compounds 34, 35, 58, and 176 of formula (I). Secondly, the Office has noted that "adjacent homologs are considered to be obvious absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art" (page 7 and 8). The claimed "adjacent" compounds of formula (I) possess an unexpected pharmacological activity that is not disclosed or suggested by Guarna-2000, thus the claimed "adjacent" compounds of formula (I) cannot be obvious because they have unexpected properties. Furthermore, Guarna-2000 teaches away from the claimed compounds because compounds 11, 12, and 13 are used as chiral auxiliaries for preparing other compounds, which are also not pharmacologically active, thus the claimed compounds cannot be obvious in view of Guarna-2000. Applicants respectfully request that this rejection be withdrawn.

Scarpi

Claims 41 and 42 are rejected under 35 U.S.C. § 103 for obviousness in view of Scarpi. The Examiner asserts that, in compound 1 on page 1627, Scarpi teaches compound 32 of formula (I), as defined in claim 25, such that making compound 33 of formula (I), as defined in claim 25, which is a stereoisomer of compound 32, is obvious.

Applicants respectfully disagree. Firstly, Applicants have disclaimed compound 32 of formula (I). Secondly, the Office has noted that "adjacent homologs are considered to be obvious

absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art" (page 7 and 8). The claimed "adjacent" compounds of formula (I) possess an unexpected pharmacological activity that is not disclosed by Scarpi, thus the claimed compounds of formula (I) cannot be obvious because of the unexpected properties of the compounds. Furthermore, Scarpi discloses the use of compound 32 to bind and change the conformation of a peptide chain, which teaches away from the use of the compounds of formula (I) as pharmacological agents, thus the "adjacent" claimed compounds of formula (I) cannot be obvious in view of Scarpi. Applicants respectfully request that this rejection be withdrawn.

Machetti

Claims 41 and 42 are rejected under 35 U.S.C. § 103 for obviousness in view of Machetti. The Examiner asserts that, in compound 1 on page 1627, Machetti teaches compound 36 of formula (I), as defined in claim 25, such that the preparation of compound 37 of formula (I), as defined in claim 25, which is a stereoisomer of compound 26, is obvious.

Applicants respectfully disagree. Firstly, Applicants have disclaimed compound 36 of formula (I). Secondly, the Office has noted that "adjacent homologs are considered to be obvious absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art" (page 7 and 8). The claimed "adjacent" compounds of formula (I) possess an unexpected pharmacological activity that is not disclosed by Machetti, thus the claimed compounds of formula (I) cannot be obvious because of the unexpected

properties of the compounds. Furthermore, Machetti teaches the use of the claimed compounds as catalysts in transesterification reactions on page 3987, column 2, last paragraph, teaching away from the use of the "adjacent" claimed compounds of formula (I) as pharmacological agent, thus the claimed compounds of formula (I) cannot be obvious. Applicants respectfully request that this rejection be withdrawn.

Guarna-1999

Claims 22-26, 41, and 42 are rejected under 35 U.S.C. § 103 for obviousness in view of Guarna-1999. The Examiner asserts that, Guarna-1999 teaches compounds comprising the 3-aza-bicyclo[3.2.1]octane core including specific exemplary compounds. For example, the Examiner asserts that, in compound 12 on page 7353, Guarna-1999 teaches compound 192 of formula (I), as defined in claim 25, as well as a general strategy for preparing all of the individual stereoisomers of the compounds comprising the 3-aza-bicyclo[3.2.1]octane core as noted in Chart 1 on page 7349 and the pharmaceutical utility of these compounds. In view of these assertions, the Examiner concludes that it would be obvious to prepare claimed compounds of formula (I) and pharmaceutical compositions containing them.

Applicants respectfully disagree. Firstly, Applicants have disclaimed compound 192 of formula (I). Secondly, the Office has noted that "adjacent homologs are considered to be obvious absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art" (page 7 and 8). The "adjacent" claimed compounds of formula (I) and pharmaceutical compositions containing them possess biological activity,

particularly that of neurotrophine agonists, which is not disclosed by Guarna-1999, therefore, the claimed compounds of formula (I) and the pharmaceutical compositions containing them cannot be obvious because they contain unexpected properties. Furthermore, Guarna-1999 does not disclose any pharmaceutical compositions or any therapeutic uses of the claimed compounds of formula (I). Additionally Guarana-1999 teaches away from the claimed invention because the compounds disclosed are used in the synthesis of modified peptides, therefore the claimed invention cannot be obvious in view of Guarana-1999. Applicants respectfully request that this rejection be withdrawn.

Provisional Obviousness-Type Double Patenting Rejection

Claims 22-26, 41, and 42 are provisionally rejected for non-statutory obviousness-type double patenting over claims 1-5 of U.S. Serial No. 10/220,556. Applicants respectfully disagree with this provisional rejection, because the claims of the present application and those of the '556 application are not identical, as acknowledged by the Examiner, and the claims are patentably distinct for the same reasons provided above in response to the Examiner's rejections of the claims for obviousness in view of Guarna-2003, which is a corresponding publication of the '556 application. Applicants thus respectfully request that this rejection be withdrawn.

Applicants further submit that, when the only rejection remaining in a case is a provisional double patenting rejection, an application should be allowed to issue. M.P.E.P. § 822.01. In view of the amendments and remarks provided herein, Applicants submit that all of the grounds of rejection in this case, other than the double patenting rejection, have been met. Accordingly, the double patenting rejection should be withdrawn and the case allowed to issue.

CONCLUSION

Applicants submit that the amended claims are in condition for allowance, and this action is hereby respectfully requested.

Enclosed are a Petition to extend the period for replying to the Office action for three months, to and including January 29, 2007 (January 27, 2007 is a Saturday), and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: January 29, 2007

Susan M. Michaud

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